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(71) Applicant *(for all designated States except US)*: **EISAI CO., LTD.** [JP/JP]; Koishikawa 4-6-10, Bunkyo-ku, Tokyo 112-8088 (JP).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BARTH, Jay** [US/US]; Glenpointe Centre West, 500 Frank W. Burr Blvd., Teaneck, NJ 07666 (US). **IENI, John** [US/US]; 253 Ridgewood Avenue, Glen Ridge, NJ 07028 (US).

(74) Agents: **GRIEFF, Edward, D.** et al.; Hale and Dorr LLP, The Willard Office Building, 1455 Pennsylvania Avenue, NW, Washington, DC 20004 (US).

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(54) Title: COMPOSITIONS AND METHODS USING PROTON PUMP INHIBITORS

(57) Abstract: The invention provides methods for treating and preventing gastrointestinal disorders, viral infections, fungal infections, Whipple's disease, sleep disorders, sleep apnea, iron deficiency anemia, asthma, nasal airway resistance, cystic fibrosis, pancreatitis, chemotherapy-induced emesis, radiation induced injury to the gastrointestinal tract, epilepsy, middle ear infections, obesity, hiatal hernia, anorexia, bulimia, dental decay, post-operative aspiration, migraines and other disorders by administering to a patient a therapeutically effective amount of at least one proton pump inhibitor. In other embodiments, the proton pump inhibitor can be administered with one or more histamine antagonists, antacids, bismuth compounds, anti-viral agents, anti-fungal agents, NSAIDs, steroids, cyclodextrins, cyclodextrin derivatives, and migraine drugs. In other embodiments, the invention provides nasally or transdermally administrable formulations comprising at least one proton pump inhibitor and, optionally, one or more histamine antagonists, antacids, bismuth compounds, anti-viral agents, anti-fungal agents, NSAIDs, steroids, cyclodextrins, cyclodextrin derivatives, and migraine drugs.

Compositions and Methods Using Proton Pump Inhibitors

Related Applications

This application claims priority to U.S. Provisional Application No. 60/449,838, filed February 27, 2003; U.S. Provisional Application No. 60/404,154, filed August 19, 2002; and U.S. Provisional Application No. 60/380,855, filed May 17, 2002, all of which are incorporated herein by reference.

Field of the Invention

The invention provides safe and effective methods for treating and preventing gastrointestinal disorders by administering at least one proton pump inhibitor. In one embodiment, the proton pump inhibitor is rabeprazole, a pharmaceutically acceptable salt thereof and/or a stereoisomer thereof.

Background of the Invention

Peptic ulcers are localized erosions of the mucous membrane of the duodenum and/or stomach which expose the underlying layers of the gut wall to the acid secretions of the stomach and to the proteolytic enzyme pepsin. Peptic ulceration is a common disease of the gastrointestinal tract and it is estimated that about 10 to 20% of the adult male population will experience peptic ulceration at some time in their lives. ACIPHEX® (Eisai, Inc., Teaneck, NJ), a proton pump inhibitor, is highly successful in treating peptic ulcers. ACIPHEX® is described in U.S. Patent No. 5,045,552, the disclosure of which is incorporated by reference herein in its entirety. There is a need in the art for new and improved treatments for peptic ulcers and other gastrointestinal disorders. The invention is directed to these, as well as other, important ends.

Summary of the Invention

The invention provides methods for treating and preventing gastrointestinal disorders, viral infections, fungal infections, Whipple's disease, sleep disorders, sleep apnea, iron deficiency anemia, asthma, nasal airway resistance, cystic fibrosis, pancreatitis, chemotherapy-induced emesis, radiation-induced injury to the gastrointestinal tract, epilepsy, middle ear infections, obesity, hiatal hernia, anorexia, bulimia, dental decay, post-operative aspiration, migraines and other disorders by administering to a patient a therapeutically effective amount of at least one proton pump inhibitor. The proton pump inhibitor can be administered with one or more histamine antagonists, antacids, bismuth compounds, anti-viral agents, anti-fungal agents, NSAIDs, steroids, and migraine drugs.

The invention provides nasally administrable formulations comprising at least one proton pump inhibitor.

The invention is described in more detail below.

Detailed Description of the Invention

The invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least two proton pump inhibitors and, optionally, a

histamine antagonist, an antacid, a bismuth compound, sucralfate, cisapride, misoprostol, or a mixture of two or more thereof. The invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and at least one histamine antagonist and, optionally, an antacid, a bismuth compound, sucralfate, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and at least one antacid and, optionally, a histamine antagonist, a bismuth compound, sucralfate, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and at least one bismuth compound and, optionally, a histamine antagonist, an antacid, sucralfate, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor, at least one histamine antagonist, and at least one antacid and, optionally, a bismuth compound, sucralfate, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor, at least one histamine antagonist, at least one antacid, and at least one bismuth compound, sucralfate, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and sucralfate and, optionally, a histamine antagonist, an antacid, a bismuth compound, cisapride, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and cisapride and, optionally, a histamine antagonist, an antacid, a bismuth compound, sucralfate, misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and/or preventing gastrointestinal disorders in a patient in need thereof by administering at least one proton pump inhibitor and misoprostol and, optionally, a histamine antagonist, an antacid, a bismuth compound, sucralfate, cisapride or a mixture of two or more thereof. In other embodiments of each of these methods, the patient can be administered at least two proton pump inhibitors, where the first proton pump inhibitor is rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof and where the second proton pump inhibitor is omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline. In other embodiments, the invention provides

methods for treating or preventing gastrointestinal disorders in a patient by administering at least one proton pump inhibitor and one or more compounds selected from the group consisting of nonsteroidal antiinflammatory drugs (NSAIDs), steroids, anti-viral agents and anti-fungal agents. The at least one proton pump inhibitor, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol can be administered separately or in the form of a composition.

The term "treating" includes eliminating the gastrointestinal disorder or future re-occurrence thereof, or reducing the severity, duration, and/or symptoms of the gastrointestinal disorder (e.g., compared to an untreated gastrointestinal disorder).

The gastrointestinal disorder can be any in the art. Exemplary gastrointestinal disorders include *H. pylori* infections, ulcers, erosive esophagitis, gastroesophageal reflux disease (GERD), erosive gastroesophageal reflux disease, gastritis, symptomatic GERD, pregnancy-induced GERD, hypersecretory conditions (e.g., Zollinger-Ellison syndrome, idopathic gastric acid hypersecretion), gastrointestinal motility disorders, Barrett's esophagus, dyspepsia, dysphagia, irritable bowel syndrome, inflammatory bowel disease, infectious enteritis, diarrhea, gastroparesis, collagenous colitis, lymphocytic colitis, short bowel syndrome, bleeding associated with short bowel syndrome, gastrointestinal bleeding, hiatal hernia, emesis, abdominal pain, and the like. "Ulcers" include peptic ulcers, bleeding peptic ulcers, stress ulcers, stomal ulcers, refractory ulcers, esophageal ulcers, fungal-induced ulcers, viral-induced ulcers, and the like. "Peptic ulcers" include gastric ulcers and duodenal ulcers. The ulcers can be associated with *H. pylori*. Inflammatory bowel disease includes Crohn's disease and ulcerative colitis. Infectious enteritis can be caused, for example, by *Campylobacter* species, *Shigella* species, *Yersinia* species (e.g., *Yersinia enterocolitica*), *Cryptosporidium* species, *Giardia* species (e.g., *Giardia lamblia*), *Salmonella* species, *Pseudomonas* species (e.g., *Pseudomonas aeruginosa*), and the like.

Any histamine antagonist, derivative or metabolite thereof can be used in the compositions and methods of the invention. Exemplary histamine antagonists include ranitidine, ranitidine/bismuth citrate, cimetidine, famotidine, nizatidine, roxatidine, ebrotidine, burimamide, tiotidine, metiamide, oxmetidine and the like.

Any antacid can be used in the compositions and methods of the invention. Exemplary antacids include calcium carbonate/magnesium hydroxide, aluminum hydroxide, magnesium hydroxide, magnesium carbonate, magnesium oxide, calcium carbonate, calcium carbonate/simethicone, aluminum hydroxide/magnesium hydroxide/simethicone, simethicone, and the like.

In other embodiments, a composition comprising at least one histamine antagonist and at least one antacid can be used in the compositions and methods of the invention. Exemplary compositions

comprising at least one histamine antagonist and at least one antacid include famotidine/calcium carbonate/magnesium hydroxide, and the like.

Any bismuth compound can be used in the compositions and methods of the invention. Exemplary bismuth compounds include bismuth citrate, bismuth salicylate, bismuth tartaric acid, and the like.

The invention provides methods for treating and/or preventing bleeding associated with or caused by short bowel syndrome by administering to a patient in need thereof at least one proton pump inhibitor. In one embodiment, the proton pump inhibitor is rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. In other embodiments, the patient can also be administered a histamine antagonist, an antacid, a bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof.

The invention provides methods for treating and preventing gastrointestinal disorders induced or caused by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one NSAID, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. The invention provides methods for treating and preventing gastrointestinal disorders induced or caused by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least two proton pump inhibitors and, optionally, at least one NSAID, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor, at least one histamine antagonist and, optionally, at least one NSAID, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor, at least one antacid and, optionally, at least one NSAID, at least one histamine antagonist, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced by NSAIDs by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor, at least one histamine agonist, at least one antacid and, optionally, at least one NSAID, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In other embodiments of each of these methods, the patient can be administered at least two proton pump inhibitors, where the first proton pump inhibitor is rabeprazole, a stereoisomer

thereof and/or a pharmaceutically acceptable salt thereof and where the second proton pump inhibitor is omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline. The gastrointestinal disorders induced or caused by NSAIDs can be any gastrointestinal disorder known in the art, such as those described herein. In one embodiment, the gastrointestinal disorder is a peptic ulcer or gastrointestinal bleeding. The at least one proton pump inhibitor, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride, misoprostol and/or at least one NSAID can be administered separately or in the form of a composition.

Any NSAID can be used in the compositions and methods of the invention. NSAIDs include COX-1 and/or COX-2 inhibitors. Exemplary COX-2 inhibitors include celecoxib, rofecoxib, valdecoxib, and the like. Exemplary NSAIDs include celecoxib, rofecoxib, valdecoxib, ibuprofen, acetaminophen, aspirin, naproxen, acetaminophen/aspirin/caffeine, ketorolac, ketoprofen, diflunisal, salsalate, salicylate, salicylamide, thiosalicylate, trisalicylate, mesalamine, sulfasalazine, methylsalicylate, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, dipyrone, azapropazone, phenacetin, indomethacin, sulindac, mefenamic, meclofenamic, flufenamic, tolfenamic, etofenamic, tolmetin, naproxen, flurbiprofen, fenoprofen, fenbufen, pirprofen, oxaprozin, indoprofen, tiaprofenic acid, piroxicam, ampiroxicam, tenoxicam, tolmetin, meloxicam, tenidap, diclofenac, diclofenac/misoprostol, sulindac, etodolac, nabumentone, and the like.

In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced or caused by steroids by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one steroid, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced or caused by steroids by administering to a patient in need thereof a therapeutically effective amount of at least two proton pump inhibitors and, optionally, at least one steroid, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders caused by steroids by administering a therapeutically effective amount of at least one proton pump inhibitor, at least one histamine antagonist, and, optionally, at least one steroid, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders caused by steroids by administering a therapeutically effective amount of at least one proton pump inhibitor, at least one antacid, and,

optionally, at least one steroid, at least one histamine antagonist, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders caused by steroids by administering a therapeutically effective amount of at least one proton pump inhibitor, at least one histamine antagonist, at least one antacid, and, optionally, at least one steroid, at least one bismuth compound, sucralfate, cisapride and misoprostol or a mixture of two or more thereof. In other embodiments of each of these methods, the patient can be administered at least two proton pump inhibitors, where the first proton pump inhibitor is rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof and where the second proton pump inhibitor is rabeprazole, omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline. In another embodiment, the invention provides methods for treating and preventing gastrointestinal disorders induced or caused by steroids by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and, optionally, at least one steroid, at least one histamine antagonist, at least one antacid, at least one bismuth compound, sucralfate, cisapride and misoprostol can be administered separately or in the form of a composition. The gastrointestinal disorders can be any known in the art, such as those described herein. In one embodiment, the gastrointestinal disorder is a peptic ulcer or GERD.

Any steroid can be used in the compositions and methods of the invention. In one embodiment, the steroids are anti-asthma medications. Exemplary steroids include alclometasone, beclomethasone, betamethasone, budesonide, clobetasol, clotrimazole/betamethasone, desonide, diflorasone, fluocinolone, fluocinolone, flurandrenolide, fluticasone, prednisone, methylprednisolone, hydrocortisone, flunisolide, hydrocortisone/pramoxine, triamcinolone, butixocort, dexamethasone, desoximetasone, halobetasol, fluocortin, tixocortal, tipredane, mometasone, prednicarbate, prednisone, and the like.

In another embodiment, the invention provides methods for treating viral infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. In another embodiment, the invention provides methods for treating viral infections by administering to a patient in need thereof a therapeutically effective amount of at least two proton pump inhibitors. In yet another embodiment, the invention provides methods for treating viral infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and at least one anti-viral agent. The proton pump inhibitor and anti-viral agent can be administered separately or in the form of a composition. The proton pump inhibitor can be rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. In other embodiments, the proton pump inhibitor can be omeprazole, lansoprazole, esomeprazole,

pantoprazole, and the like.

Exemplary viral infections include herpes (e.g., HSV-1, HSV-2, CMV, Epstein Barr, herpes zoster); HIV disease (e.g., AIDS); hepatitis (e.g., hepatitis A, hepatitis B, hepatitis C); and the like. Any anti-viral agent can be used in the compositions and methods of the invention. Exemplary anti-viral agents include acyclovir, amprenavir, interferon, nevirapine, famciclovir, rimantadine, amantadine, palivizumab, oseltamivir, valcyclovir, metronidazole, didanosine, ddI, ddC, 3TC, d4T, epivir, zidovudine, lamivudine, abacavir, tenofovir, indinavir, valganciclovir, ganciclovir, abacavir/lamivudine/zidovudine, lamivudine/zidovudine, saquinavir, foscarnet, zalcitabine, ritonavir, ribavirin, ribavirin/interferon, zanamivir, delavirdine, nelfinavir, efavirenz, stavudine, β-L-Fd4C, pyrimethamine, atovaquone, rifabutin, and the like. One skilled in the art would appreciate which particular anti-viral agents would be used for any particular viral infection.

In another embodiment, the invention provides methods for treating fungal infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. In another embodiment, the invention provides methods for treating fungal infections by administering to a patient in need thereof a therapeutically effective amount of at least two proton pump inhibitors. In yet another embodiment, the invention provides methods for treating fungal infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor and at least one anti-fungal agent. In yet another embodiment, the invention provides methods for treating fungal infections by administering to a patient in need thereof a therapeutically effective amount of at least two proton pump inhibitors and, optionally, at least one anti-fungal agent, where the first proton pump inhibitor is rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof, and the second proton pump inhibitor is omeprazole, lansoprazole, esomeprazole or pantoprazole. The proton pump inhibitor and anti-fungal agent can be administered separately or in the form of a composition. The proton pump inhibitor can be rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof.

Any anti-fungal agent can be used in the compositions and methods of the invention. Exemplary anti-fungal agents include ketoconazole, diflucan, terbinafine, itraconazole, flucytosine, caspofungin, griseofulvin, clotrimazole, miconazole, fluconazole, 5-fluoro-cytosine, griseofulvin, tioconazole, amphotericin B, and the like.

In other embodiments, the invention provides methods for treating and preventing Whipple's disease in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor. Whipple's disease is a malabsorption disease that interferes with the body's ability to absorb certain nutrients. Whipple's disease can cause weight loss, irregular breakdown of carbohydrates and fats, resistance to insulin, and malfunctions of the immune system. Symptoms of Whipple's disease include diarrhea, intestinal bleeding, abdominal bloating and cramps, loss of

appetite, weight loss, fatigue, and weakness.

In other embodiment, the invention provides methods for treating and preventing sleep disorders secondary to GERD by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. Sleep disorders secondary to GERD can include REM disorders, sleep deprivation, REM-deprived sleep disorders, and insomnia.

In other embodiments, the invention provides methods for treating and preventing one or more symptoms associated with or caused by sleep apnea by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. Patients with sleep apnea stop breathing repeatedly during their sleep, often for a minute or longer, and as many as hundreds of times during a single night. In one embodiment, the sleep apnea is obstructive sleep apnea syndrome or obstructive sleep apnea, which is caused by a complete and/or partial obstruction of the patient's airway. Partial obstructive sleep apnea can also be called obstructive hypopnea; where hypopnea is slow, shallow breathing. Physical signs that suggest obstructive sleep apnea syndrome or obstructive sleep apnea include loud snoring, witnessed apneic episodes, obesity, excessive daytime sleepiness, and nocturnal snorting and gasping

In other embodiments, the invention provides methods for treating and preventing one or more symptoms associated with iron deficiency anemia by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. The following are the most common symptoms of iron-deficiency anemia: abnormal paleness or lack of color of the skin; irritability; fatigue (e.g., lack of energy or tiring easily); tachycardia; sore or swollen tongue; enlarged spleen; and/or a desire to eat peculiar substances, such as dirt or ice (e.g., pica).

In other embodiments, the invention provides methods for decreasing nasal airway resistance and increasing nasal air flow by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. In other embodiments, the invention provides methods for decreasing nasal airway resistance during exercise by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating asthma by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing cystic fibrosis by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. The patient can be an adult or a child. Cystic fibrosis is a disorder of the cells that line the lungs, small intestines, sweat glands and pancreas, where mucus contributes to the destruction of lung tissue.

In other embodiments, the invention provides nutrient absorption in the small intestines, and blocks pancreatic ducts from releasing digestive enzymes. Symptoms of cystic fibrosis include

excessive appetite, poor weight gain, diarrhea, persistent cough, and other digestive disorders.

In other embodiments, the invention provides methods for treating and preventing pancreatitis by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. Pancreatitis is an inflammation of the pancreas which can be acute or chronic. Symptoms of pancreatitis can include a swollen and tender abdomen, nausea, vomiting, fever and a rapid pulse.

In other embodiments, the invention provides methods for treating and preventing chemotherapy-induced emesis by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. The proton pump inhibitor can be administered before, during and/or after chemotherapy.

In other embodiments, the invention provides methods for treating and preventing radiation-induced injury to the gastrointestinal tract by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing epilepsy or other seizure disorders by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. Epilepsy, sometimes called a seizure disorder, is a chronic medical condition produced by temporary changes in the electrical function of the brain, causing seizures which affect awareness, movement and/or sensation.

In other embodiments, the invention provides methods for treating and preventing middle ear infections by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. A middle ear infection (otitis media) is an inflammation of the area behind the eardrum. The proton pump inhibitors can be administered systemically to treat middle ear infections. In another embodiment, the proton pump inhibitors can be administered aurally, orally or by nasal inhalation to treat middle ear infections.

In other embodiments, the invention provides methods for treating patients who have had esophageal bypass surgery by administering a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing obesity by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor. In still other embodiments, the invention provides methods for treating patients who have had surgery for obesity (e.g., laparoscopic obesity surgery, bariatric surgery, gastric surgery, gastric bypass surgery) by administering a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing a hiatal hernia by administering to a patient in need thereof a therapeutically effective amount of at least one

proton pump inhibitor. A hiatal hernia occurs when the upper part of the stomach moves up into the chest through a small opening in the diaphragm, e.g., diaphramgatic hiatus. The hiatal hernia can result in retention of acid and other contents above the opening which reflux into the esophagus.

In other embodiments, the invention provides methods for treating and preventing belching, eructation and/or flatulence by administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing eating disorders (e.g., anorexia or bulimia) in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor. In another embodiment, the invention provides methods for treating the gastrointestinal injuries, esophageal injuries, and/or dental decay caused by bulimia in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing dental decay or erosion of tooth enamel in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor.

In other embodiments, the invention provides methods for treating and preventing post-operative aspiration and/or post-operative ulcers in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor. Administering at least one proton pump inhibitor prior to surgery will reduce gastric pH, which will reduce or eliminate the occurrence of post-operative aspiration or will reduce or eliminate the likelihood of post-operative ulcers occurring as a result of post-operative aspiration.

In other embodiments, the invention provides methods for treating and preventing erosive gastrointestinal reflux disease (GERD) in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor, optionally in combination with one or more histamine antagonists, antacids, bismuth compounds, or mixtures of two or more thereof. GERD occurs when stomach acid moves in the wrong direction, flowing back up (reflux) into the esophagus causing one or more symptoms of heartburn, coughing, wheezing, hoarseness, regurgitation, epigastric pain, dysphagia, and chest pain. Over time, reflux of acid can erode the lining of the esophagus, leading to inflammation and ulcers, a condition called erosive GERD.

In another embodiment, the invention provides methods for increasing gastric mucin production in a patient in need thereof by administering a therapeutically effective amount of at least one proton pump inhibitor. The proton pump inhibitor is preferably rabeprazole, a stereoisomer thereof and/or a pharmaceutically acceptable salt thereof. It has been unexpectedly discovered that proton pump inhibitors, such as rabeprazole, increase the content of gastric mucin in the patient's stomach. The increased gastric mucin enhances the protective properties of the mucous barrier in the

stomach and can also protect the upper alimentary tract mucosa.

In another embodiment, the invention provides methods for preventing and treating migraines by administering a therapeutically effective amount of at least one proton pump inhibitor. In another embodiment, the invention provides methods for preventing and treating migraines by administering a therapeutically effective amount of at least two proton pump inhibitors. In another embodiment, the invention provides methods for preventing and treating migraines by administering a therapeutically effective amount of at least one proton pump inhibitor and at least one migraine drug. The proton pump inhibitor and migraine drug can be administered separately or in the form of a composition.

The migraines can be classic migraines, common migraines, complicated migraines, and/or cluster headaches. In other embodiments, the migraines can be menstrual migraines, premenstrual migraines, ophthalmic migraines, and/or ophthalmoplegic migraines. In other embodiments, the migraines can be fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. In still other embodiments, the migraines can be abdominal migraines.

"Migraine" refers to periodic, hemicranial, throbbing headaches that can be accompanied by nausea and/or vomiting. Migraines can occur in children and adults, and men and women. "Migraine" includes classic migraines, common migraines, complicated migraines, cluster headaches, menstrual migraines, premenstrual migraines, ophthalmic migraines, ophthalmoplegic migraines, fulgurating migraines, Harris' migraines, and/or hemiplegic migraines. Neurologic symptoms can occur which are caused by migraines, bur which are not followed by a headache. For example, abdominal pain and vomiting can occur without headache as the sole expression of a migraine. "Classic migraines" generally begin with neurologic symptoms such as visual scintillations, dazzling zigzag lines, photophobia and spreading scotomas, or dizziness and tinnitus. Classic migraines can have premonitory symptoms such as feelings of elation, excessive energy, thirst, cravings for sweets, and/or drowsiness. At other times, classic migraines can have premonitory symptoms such as a slowing of mentation, a feeling of impending doom, and/or depression. At other times, there can be no premonitory symptoms. "Common migraines" generally have an unheralded onset of headache that can be accompanied by nausea and/or vomiting. Unlike the classic migraine, the common migraine generally does not have neurologic symptoms that occur prior to the onset of the headache. "Complicated migraines" refers to migraines accompanied by neurologic symptoms (e.g., such as those described for classic migraines) that can either precede or accompany the headache. In complicated migraines, numbness and tingling of the lips, face, hand, arm, and/or leg on side of the body can occur, sometimes in combination with aphasic disorder. The arm and/or leg can become weak or paralyzed on one side, mimicking a stroke. The numbness or weakness can spread from one part of the body to another slowly over a period of minutes. "Complicated migraines" include basilar migraines. In basilar migraines, the visual disorder and paresthesias are bilateral and can be

accompanied by confusion, stupor, coma, aggressive outbursts, vertigo, diplopia, and/or dysarthria. Basilar migraines occur in 30% of children with migraines. "Cluster headaches" are also called paroxysmal nocturnal cephalalgia, migrainous neuralgia, histamine headache, and Horton's syndrome. Cluster headaches are characterized by constant, unilateral orbital pain, with onset usually within two or three hours after falling asleep. The pain can be intense and steady with lacrimation, blocked nostril, then rhinorrhea, and sometimes miosis, ptosis, flush, and edema of cheek. "Menstrual migraines" refer to migraine headaches that can generally occur from about two days prior to a woman's menstrual cycle until about three days after a woman's menstrual cycle. In another embodiment, menstrual migraines refer to migraine headaches that can generally occur from about two days prior to a woman's menstrual cycle and that generally end on the last day of the woman's menstrual cycle. Menstrual migraines can occur or re-occur at any time during the menstrual cycle. "Premenstrual migraines" are migraine headaches that can generally occur from about seven days prior to a woman's menstrual cycle to about three days prior to a woman's menstrual cycle. Premenstrual migraines can occur or re-occur at any time during the premenstrual cycle. "Ophthalmic migraines" are migraine headaches that are generally accompanied by a marked disturbance of vision. "Ophthalmoplegic migraines" are migraine headaches associated with paralysis of the eye muscles. "Fulgurating migraines" are migraine headaches characterized by an abrupt beginning and severity. "Harris' migraine" is also known as periodic migrainous *neuralgia*. "Hemiplegic migraines" are a form of migraine headache associated with transient hemiplegia. "Abdominal migraines" are characterized by paroxysmal abdominal pain without apparent cause. "Treating" refers to eliminating the migraine or alleviating the symptoms of the migraine (e.g., compared to the symptoms prior to administering one or more proton pump inhibitors and, optionally, one or more migraine drugs). Treating encompasses alleviating the number of migraines, the intensity of the migraines and/or the duration of the migraines.

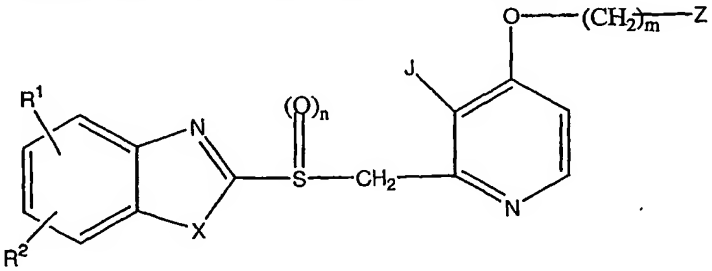
Migraine drugs that can be used to prevent and/or treat migraines include, for example, estrogen, serotonin antagonists, non-steroidal antiinflammatory drugs (NSAIDs) (e.g., COX-1 inhibitors and/or COX-2 inhibitors), calcium channel blockers, beta-andrenergic blockers, anticonvulsants, and antidepressants (e.g., tricylcic antidepressants, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors). Estrogen is generally used for preventing and/or treating menstrual migraines and premenstrual migraines.

Exemplary migraine drugs that can be used to prevent and/or treat migraines include celecoxib, valdecoxib, meloxicam, etodolac, rofecoxib, PNU-142633, vigabatrin, topiramate, montelukast (e.g., the sodium salt thereof), gabapentin, piroxicam (e.g., piroxicam betadex), valproate (e.g., the semisodium salt thereof), ketoprofen, diclofenac (e.g., the potassium salt), tiagabine, botulinum, nebivolol, lisinopril, nimodipine, tizanidine, zolmitriptan, sumatriptan (e.g., the succinate

salt thereof), rizatriptan (e.g., the benzoate salt thereof), pizotifen, oxetorone, naratriptan, lomerizine (e.g., the hydrochloride salt thereof), gepefrine, flunarizine, almotriptan, alpiropride, tolfenamic acid, migpriv, timolol (e.g., the maleate salt thereof), buclizine (e.g., the hydrochloride salt thereof), baclofen, methysergide (e.g., the maleate salt thereof), flunarizine (e.g., the hydrochloride salt thereof), cyproheptadine (e.g., the hydrochloride salt thereof), ergotamine (e.g., the tartrate salt thereof), lidocaine (e.g., the hydrochloride salt thereof), indoramin (e.g., the hydrochloride salt thereof), butorphanol, KT 2962, BMS 181885, ADDS-ergotamine, NPS-1776, GW-468816, triptan, Pharmaprojects No. 6313, MT-500, donitriptan (e.g., the mesylate salt thereof), ALX-0646, civamide, propanolol, zucapsaicin, CNS 5161, vofopitant, lanepitant, dapitant, ganaxolone, LY-53857, sergolexole (e.g., the maleate salt thereof), sumatriptan, MT-400, fluoxetine, (S)-fluoxetine, dihydroergotamine (e.g., the mesylate salt thereof), tonabersat, IS-159, BIBN-4096, metoclopramide, naproxen, MT-100 (e.g., a combination of metoclopramide and naproxen), dotarizine, frovatriptan, eletriptan, aspirin, ibuprofen, acetaminophen, amitryptiline, doxepin, ergot preparations, caffeine, cafergot (e.g., a combination of caffeine and ergotamine), codeine, meperidine, promethazine, atropine, phenobarbital, nifedipine, verapamil, chlorpromazine, lithium, prednisone, propranolol, phenelzine, mefenamic acid, flufenamic acid, LY334370, indomethacin, dichloralphenazone, isometheptene, butalbital, ketorolac, clonazepam, atenolol, metoprolol, nadolol, imipramine, nortripyline, diltiazem, valproic acid, divalproex, cyproheptadine, or pharmaceutically acceptable salts thereof.

Any proton pump inhibitor can be used in the compositions and methods described herein. Exemplary proton pump inhibitors include rabeprazole, omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline, and the like.

In one embodiment, the proton pump inhibitors are compounds of formula (I), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:



(I)

wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group;

X is -O-, -S- or =N-R^3, wherein R^3 is a hydrogen atom or a lower alkyl, phenyl, benzyl or

lower alkoxycarbonyl group; and

Z is:

1. $-O(CH_2)_p-O-R^4$

wherein p is an integer of 1 to 3 and R^4 is hydrogen atom or a lower alkyl, aryl or aralkyl group,

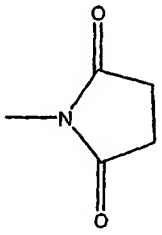
2. $-O-(CH_2)_q-R^5$

wherein q is an integer of 1 to 3 and R^5 is a halogen atom or an alkoxycarbonyl, aryl or heteroaryl group,

3. $-O-(CH_2)_r-O-(CH_2)_s-O-R^6$

wherein r and s are each independently an integer of 1 to 5 and R^6 is a hydrogen atom or a lower alkyl group,

4.



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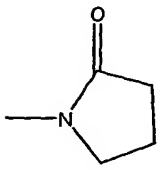

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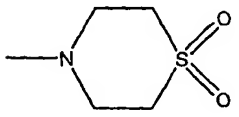
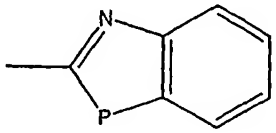
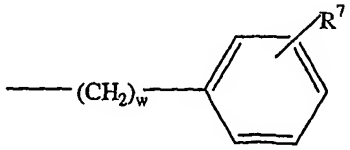


7. $-S(O)_t-A$

wherein t is an integer of 0 to 2, and A is a lower alkyl, alkoxycarbonylmethyl, pyridyl, furyl,



or



wherein B is -NH-, -O- or -S-, and w is an integer of 0 or 1;

8. $-N(R^8)-CH_2-C_6H_5$

wherein R^8 is an acetoxy or lower alkyl group;

9. $-OR^9$

wherein R^9 is a hydrogen atom, a lower alkyl or aryl group;

n is an integer of 0 to 2; m is an integer of 2 to 10, and J and K are each independently a hydrogen atom or a lower alkyl group, with the proviso that when Z is a group falling under the above category (9), then R^9 is a lower alkyl group and m stands for an integer of 3 to 10, and pharmaceutically acceptable salts thereof.

The same definitions for R^1, R^2, X, n, J, K, Z and m are used throughout the specification that follows and in the appended claims.

Also disclosed are pharmaceutical compositions containing one or more of these compounds as the active ingredient(s) in a pharmaceutically acceptable carrier, adjuvant or vehicle.

In the definition of the compounds of formula (I), the lower alkyl group defined with respect to R^1, R^2, R^3, R^4, R^6, R^7, R^8, A, J and K can be a straight-chain or branched alkyl group having 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, n-butyl, isopropyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl groups, among which methyl and ethyl groups are most preferred.

The lower alkoxy group and the lower alkoxy moiety of the lower alkoxycarbonyl group defined above with respect to R^1 and R^2 can be an alkoxy group derived form the above lower alkyl group. Methoxy and ethoxy groups are most preferred.

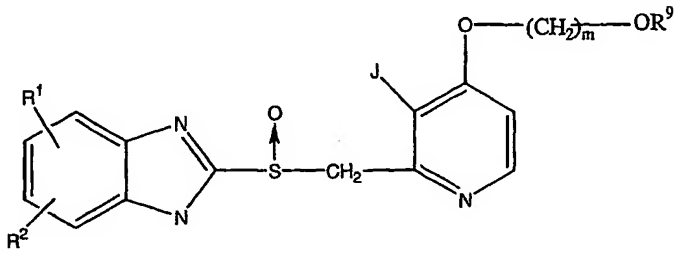
The halogen atom defined above includes chlorine, bromine, iodine or fluorine. The aryl group defined above with respect to R^4 and R^5 can be phenyl, tolyl, xylyl, napthyl or the like, which can be substituted with a lower alkoxy or hydroxyl group, a halogen atom or the like.

Examples of the arylalkyl defined above with respect to R^4 include benzyl and phenethyl groups.

Examples of the heteroaryl group defined above with respect to R^5 include pyridyl and furyl groups.

In the definition of Z in formula (I), groups 1, 2, 3, 4, 5 and 9 are preferred; and group 9 is the most preferred. As for R^1 and R^2, hydrogens for both and then a combination of a lower alkyl (e.g., methyl) for R^1 and hydrogen for R^2 are preferred. X is preferably $=NR^3$, where R^3 is hydrogen. A preferred value for n is 1. The preferred substituents for J and K are both hydrogen or where J is lower alkyl (e.g., methyl), and K is hydrogen, or when J is hydrogen and K is lower alkyl (e.g., methyl). Thus, J or K are independently preferably hydrogen or methyl, most preferably J is methyl and K is hydrogen.

In another embodiment, the compounds of formula (I) are compounds of formula (A), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:



(A)

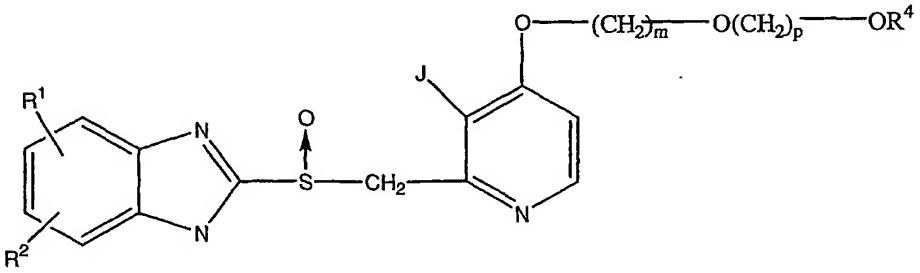
wherein R^1, R^2, J, m and R^9 have the same meanings as defined above.

In formula (A), the preferred R^1 and R^2 substituents are both hydrogen, or R^1 is 5-lower alkoxy, 5- lower alkyl or 5-halogenated lower alkyl and R^2 is hydrogen. The preferred substituent for J is hydrogen or methyl; the preferred value for m is in the range of 3 to 10, the most preferred being 3; and the preferred R^9 substituent is lower alkyl (e.g., methyl), or aryl. Among these possibilities for the compounds of formula (A), the preferred combination is when R^1 and R^2 are both hydrogen, J is methyl, m is 3 and R^9 is methyl.

Another group of preferred compounds in formula (A) are combinations of the above substituents where both R^1 and R^2 are hydrogen, J is hydrogen, m is 3 and R^9 is methyl.

Another group of preferred compounds falling within formula (A) is when both R^1 and R^2 are hydrogen, J is methyl, m is 2 and R^9 is benzyl.

In another embodiment, the compounds of formula (I) are compounds of formula (B), pharmaceutically acceptable salts thereof, and/or stereoisomers thereof:



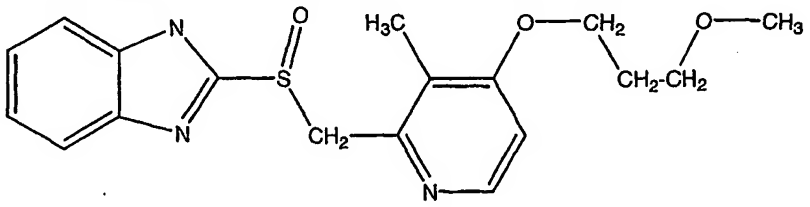
(B)

wherein R^1, R^2, J, p, m and R^4 have the same meanings as given above.

In formula (B), the preferred substituents for R^1 and R^2 are both hydrogen; or when R^1 is 5-lower alkoxy, 5-lower alkyl or 5- halogenated lower alkyl, R^2 is hydrogen. The preferred value of m is 2 or 3; the preferred value for p is 2 or 3; and the preferred substituent for R^4 is methyl or benzyl. Of the above possibilities for formula (B), the most preferred combination is

where R^1 is 5- methyl, R^2 is hydrogen, J is methyl, m is 2, p is 2 and R^4 is methyl.

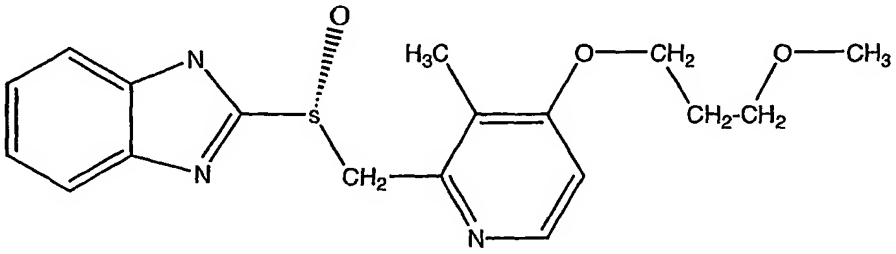
In another embodiment, the compound of formula I is a compound of formula (C), a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof:



(C).

Preferably, the compound of formula (C) is a sodium salt, which is known as rabeprazole sodium or ACIPHEX® (Eisai Inc., Teaneck, NJ).

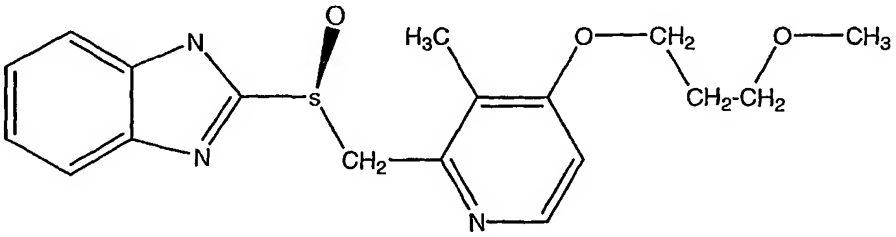
Although the compounds of the invention can be present as a hydrate or as a stereoisomer, the hydrates and stereoisomers are included within the scope of the invention. For example, the compound of formula (C) can be a compound of formula (D) or a pharmaceutically acceptable salt thereof (e.g., a sodium salt):



(D)

The compound of formula (D) is R (+) rabeprazole.

Alternatively, the compound of formula (C) can be a compound of formula (E) or a pharmaceutically acceptable salt thereof (e.g., a sodium salt):



(E)

The compound of formula (E) is S (-) rabeprazole.

The compounds of the invention can be administered as any pharmaceutically acceptable salt known in the art. Pharmaceutically acceptable salts are known in the art and

include those of inorganic acids, such as hydrochloride, sulfate, hydrobromide, sulfate, and phosphate; those of organic acids, such as formate, acetate, maleate, tartrate, trifluoroacetate, methanesulfonate, benzenesulfonate and toluenesulfonate, and those of amino acids such as arginine, aspartic acid and glutamic acid. When certain substituents are selected, the compounds of the invention can form, for example, alkali metal salts, such as sodium or potassium salts; alkaline earth metal salts, such as calcium or magnesium salts; organic amine salts, such as a salt with trimethylamine, triethylamine, pyridine, picoline, dicyclohexylamine or N,N'-dibenzylethylenediamine. One skilled in the art will recognize that the compounds of the invention can be made in the form of any of these or of any other pharmaceutically acceptable salt. For example, compounds represented by formula (I), wherein X is =N-R^3 and R^3 is a hydrogen atom, or compounds represented by formula (I), wherein Z is a group falling under the category 7 and B is a group of -NH-, can be present as a metal salt, such as sodium, potassium, magnesium or calcium.

The proton pump inhibitors are commercially available or can be prepared by processes known in the art. Rabeprazole sodium is commercially available as ACIPHEX® from Eisai Inc., Teaneck, NJ, and is described, for example, in U.S. Patent No. 5,045,552, the disclosure of which is incorporated by reference herein in its entirety. Methods for preparing R (+) rabeprazole are described in WO 99/55157, the disclosure of which is incorporated by reference herein in its entirety. Methods for preparing S (-) rabeprazole are described in WO 99/55158, the disclosure of which is incorporated by reference herein in its entirety.

A therapeutically effective dosage regimen for treating the diseases described herein with the proton pump inhibitors and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, steroids, migraine drugs, anti-viral agents and/or anti-fungal agents is selected in accordance with a variety of factors, including the age, weight, sex, and medical condition of the patient, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular proton pump inhibitor and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, steroids, migraine drugs, anti-viral agents and/or anti-fungal agents, whether a drug delivery system is used and whether the proton pump inhibitor and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, migraine drugs, steroids, anti-viral agents and/or anti-fungal agents is administered as part of a drug combination.

When administered separately, the proton pump inhibitors and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, migraine drugs,

steroids, anti-viral agents and/or anti-fungal agents can be administered about the same time as part of an overall treatment regimen, i.e., as a combination therapy or drug cocktail. "About the same time" includes administering the proton pump inhibitor and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, steroids, migraine drugs, anti-viral agents and/or anti-fungal agents at the same time, at different times on the same day, or on different days, as long as they are administered as part of an overall treatment regimen.

The proton pump inhibitors can be administered in amounts of about 0.01 to about 200 mg per day, preferably about 0.05 to about 50 mg per day, more preferably about 0.1 to about 40 mg per day, still more preferably about 10 to about 30 mg per day, still more preferably about 10 to about 20 mg per day. The compounds and/or compositions can be administered once a day or in divided doses, for example from 2 to 4 times a day, preferably once per day. One skilled in the art will recognize that when the compounds and/or compositions of the invention are administered to infants or children, the dose can be smaller than the dose administered to adults, and that the dose can be dependent upon the size and weight of the patient.

In preferred embodiments of the methods described herein, rabeprazole sodium, which is commercially available as ACIPHEX® (Eisai Inc., Teaneck, NJ), is administered as a tablet containing 10 or 20 milligrams rabeprazole sodium. The tablets can be administered one to about four times a day. In preferred embodiments, one 20 milligram ACIPHEX® tablet is administered once a day for the methods described herein. One skilled in the art will appreciate that when rabeprazole sodium is administered to infants or children, the dose can be smaller than the dose that is administered to adults.

In other embodiments, the proton pump inhibitors can be administered intermittently for the treatment of gastroesophageal reflux disease (GERD), symptomatic GERD, or symptomatic duodenal ulcer disease. Intermittent administration can also be called intermittent therapy and refers to a short course of therapy for the treatment of GERD, symptomatic GERD or symptomatic duodenal ulcer disease. Intermittent therapy can be used for patients who are experiencing GERD, symptomatic GERD, or symptomatic duodenal ulcer disease for the first time. Preferably, intermittent therapy is used for patients who have relapsed after previously recovering from GERD, symptomatic GERD, or symptomatic duodenal ulcer disease. Short course therapy refers to the administration of one daily dose of the proton pump inhibitor for a period of about 2 days to about 14 days; preferably about 2 days to about 10 days; more preferably for about 2, 3, 4, 5, 6, 7, 8 or 9 days; more preferably for about 5, 6 or 7 days; still

more preferably for about 7 days. It has been unexpectedly discovered that intermittent therapy with proton pump inhibitors for the treatment of GERD, symptomatic GERD or symptomatic duodenal ulcer disease is effective in the long-term control and maintenance of the disease. Intermittent therapy is a safe and effective alternative to continuous treatment to achieve satisfactory control of the symptoms of GERD, symptomatic GERD or symptomatic duodenal ulcer disease that avoids over-medicating the patient and that reduces the costs associated with purchasing the medications.

The histamine antagonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, steroids, migraine drugs, anti-viral agents and/or anti-fungal agents can be prepared by processes known in the art or can be obtained from commercial sources, and can be administered in therapeutically effective doses that are known in the art, such as those described in the *Physician's Desk Reference*.

The proton pump inhibitors and/or histamine agonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, steroids, migraine drugs, anti-viral agents and/or anti-fungal agents can be administered orally, topically, parenterally, by inhalation (nasal, oral, aural), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous, intravenous, intramuscular, intrathecal, intrasternal injection, or infusion techniques. Preferably, the proton pump inhibitors are orally administered as tablets.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions can be formulated according to the known art using suitable dispersing or wetting agents, suspending agents (e.g., methylcellulose, Polysorbate 80, hydroxyethylcellulose, acacia, powdered tragacanth, sodium carboxymethylcellulose, polyoxytehylene sorbitan monolaurate and the like), pH modifiers, buffers, solubilizing agents (e.g., polyoxyethylene hydrogenated castor oil, Polysorbate 80, nicotinamide, polyoxyethylene sorbitan monolaurate, Macrogol, an ethyl ester of castor oil fatty acid, and the like), preservatives and/or stabilizers. The sterile injectable preparation can also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be used are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally used as a solvent or suspending medium. For this purpose any bland fixed oil can be used including synthetic mono- or diglycerides, in addition, fatty acids such as oleic acid find use in the preparation of injectables. The preparations can be lyophilized by methods known in the art.

Solid dosage forms for oral administration can include capsules, tablets, sublingual tablets, powders, granules, gels, effervescent tablets, effervescent wafers, effervescent capsules, and effervescent powders; most preferably tablets. The solid dosage form can be a solid microencapsulated dosage, such as a microencapsulated powder, microencapsulated granules or a microencapsulated gel. A solid dosage form for oral administration can be prepared by mixing an active principle with filler and, if necessary, binder, disintegrating agent, lubricant, coloring agent, corrigent or the like and converting the obtained mixture into a tablet, coated tablet, granule, powder or capsule. Examples of the filler include lactose, corn starch, sucrose, glucose, sorbitol, crystalline cellulose and silicon dioxide, while those of the binder include polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. Examples of the disintegrating agent include starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin, while those of the lubricant include magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. The coloring agent can be any one which is permitted to be added to drugs. Examples of the corrigent include cacao powder, mentha herb, aromatic powder, mentha oil, borneol and powdered cinnamon bark. The tablets and granules can be, if necessary, coated with sugar, gelatin or the like. Preferably, the tablets have an enteric coating.

The proton pump inhibitor can be formulated or admixed with, for example, an acid (e.g., citric acid) and a bicarbonate (e.g., sodium bicarbonate) to form an effervescent tablet, capsule, wafer or powder. After addition of the effervescent tablet, capsule, wafer or powder to a liquid (e.g., water, juice) a bicarbonate solution of the proton pump inhibitor is formed.

In other embodiments, the solid dosage form can be packaged as granules or a powder in a pharmaceutically acceptable carrier, where the granules or powder are removed from the packaging and sprinkled on food or mixed with a liquid, such as water or juice. In this embodiment, the active compound can be mixed with flavoring or sweetening agents. The packaging material can be plastic, polyester films, nylon films, polyolefin films, shrink packing films, coated paper, or any material that prevents water or moisture from reaching the granules and/or powder.

Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, and syrups containing inert diluents commonly used in the art, such as water. The liquid dosage form can be a microencapsulated liquid, including microencapsulated emulsions, microencapsulated solutions, microencapsulated suspensions and microencapsulated syrups. Such compositions can also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

In another embodiment, the invention provides compositions comprising at least one proton pump inhibitor and at least one cyclodextrin or a cyclodextrin derivative. The compositions can be in the form of a sachet, granules, micro-pellets, or beads. Cyclodextrin derivatives are described, for example, in U.S. Patent No. 3,459,731, EP-A-149,197, EP-A-197,571, U.S. Patent No. 4,535,152 or WO 90/12035. Cyclodextrin derivatives include alpha-cyclodextrins, beta-cyclodextrins, and gamma-cyclodextrins. The cyclodextrins can be ethers and/or mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6} alkyl (e.g., methyl, ethyl or isopropyl); hydroxy C_{1-6} alkyl (e.g., hydroxyethyl, hydroxypropyl or hydroxybutyl); carboxy C_{1-6} alkyl (e.g., carboxymethyl or carboxyethyl); C_{1-6} alkyl-carbonyl (e.g., acetyl); C_{1-6} alkyloxycarbonyl C_{1-6} alkyl or carboxy C_{1-6} alkyl-oxy C_{1-6} alkyl (e.g., carboxymethoxypropyl or carboxyethoxypropyl); C_{1-6} alkylcarbonyloxy C_{1-6} alkyl (e.g., 2-acetyloxypropyl). In one embodiment, complexants and/or solubilizers for the proton pump inhibitors are beta-cyclodextrin; 2,6-dimethyl-beta-cyclodextrin, 2-hydroxyethyl-beta-cyclodextrin, 2-hydroxyethyl-gamma-cyclodextrin, 2-hydroxypropyl-gamma-cyclodextrin and (2-carboxy-methoxy)propyl-beta-cyclodextrin. and in particular 2-hydroxypropyl-beta-cyclodextrin. In another embodiment, the cyclodextrin is beta-cyclodextrin.

For administration by aural, oral or nasal inhalation, the compounds and compositions can be delivered from an insufflator, a nebulizer or a pressured pack or other convenient mode of delivering an aerosol spray. Pressurized packs can include a suitable propellant. Alternatively, for administration by aural, oral or nasal inhalation, the compounds and compositions can be administered in the form of a dry powder composition or in the form of a liquid spray.

Suppositories for rectal administration can be prepared by mixing one or more compounds or compositions with suitable nonirritating excipients, such as cocoa butter and/or polyethylene glycols, that are solid at room temperature and that melt at body temperature. Alternatively, enemas can be used to for rectal administration of the active compounds.

For topical administration to the epidermis, the proton pump inhibitors can be formulated as ointments, creams or lotions, or as the active ingredient of a transdermal patch. The compounds and compositions can also be administered via iontophoresis or osmotic pump. Ointments, creams and lotions can be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Alternatively, ointments, creams and lotions can be formulated with an aqueous or oily base and can also contain one or more emulsifying agents, stabilizing agents, dispersing agents, suspending agents, thickening agents, and/or coloring agents. As creams or lotions, the proton pump inhibitors can be mixed to form a smooth, homogeneous cream or lotion with, for example, one or more of a preservative (e.g., benzyl alcohol 1% or 2% (wt/wt)), emulsifying wax, glycerin, isopropyl palmitate, lactic acid, purified water, sorbitol solution. Such topically administrable compositions can

contain polyethylene glycol 400. To form ointments, the proton pump inhibitors can be mixed with one or more of a preservative (e.g., benzyl alcohol 2% (wt/wt)), petrolatum, emulsifying wax, and Tenox (II) (e.g., butylated hydroxyanisole, propyl gallate, citric acid, propylene glycol). Woven pads or rolls of bandaging material, e.g., gauze, can be impregnated with the transdermally administrable compositions for topical application.

The proton pump inhibitors can also be topically applied using a transdermal system, such as one of an acrylic-based polymer adhesive with a resinous crosslinking agent impregnated with the proton pump inhibitors and laminated to an impermeable backing. For example, the proton pump inhibitors can be administered in the form of a transdermal patch, such as a sustained-release transdermal patch. Transdermal patches can include any conventional form such as, for example, an adhesive matrix, a polymeric matrix, a reservoir patch, a matrix- or monolithic-type laminated structure, and are generally comprised of one or more backing layers, adhesives, penetration enhancers, and/or rate-controlling membranes. Transdermal patches generally have a release liner which is removed to expose the adhesive/active ingredient(s) prior to application. Transdermal patches are described in, for example, U.S. Patent Nos. 5,262,165, 5,948,433, 6,010,715 and 6,071,531, the disclosures of which are incorporated by reference herein in their entirety.

The invention provides for the proton pump inhibitors and, optionally, other active ingredients, to be administered nasally to a patient to treat the diseases and disorders described herein and those described, for example, in PCT Application No. PCT/US02/36857, the disclosure of which is incorporated by reference herein in its entirety. "Administered nasally" or "nasal administration" is intended to mean that at least one proton pump inhibitor is combined with a suitable delivery system for absorption across the nasal mucosa of a patient, preferably a human.

The proton pump inhibitors of the invention can be administered, for example, as nasal sprays, nasal drops, nasal suspensions, nasal gels, nasal ointments, nasal creams or nasal powders. The proton pump inhibitors can also be administered using nasal tampons or nasal sponges. The proton pump inhibitors of the invention can be brought into a viscous basis via systems conventionally used, for example, natural gums, methylcellulose and derivatives, acrylic polymers (carbopol) and vinyl polymers (polyvinylpyrrolidone). In the compositions, many other excipients known in the art can be added such as water, preservatives, surfactants, solvents, adhesives, antioxidants, buffers, bio-adhesives, viscosity enhancing agents and agents to adjust the pH and the osmolarity.

The nasal delivery systems can take various forms including aqueous solutions, non-aqueous solutions and combinations thereof. Aqueous solutions include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous solutions include, for example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions

and combinations thereof.

In other embodiments, the nasal delivery system can be a powder formulation. Powder formulations include, for example, powder mixtures, powder microspheres, coated powder microspheres, liposomal dispersions and combinations thereof. Preferably, the powder formulation is powder microspheres. The powder microspheres are preferably formed from various polysaccharides and celluloses selected from starch, methylcellulose, xanthan gum, carboxymethylcellulose, hydroxypropyl cellulose, carbomer, alginate polyvinyl alcohol, acacia, chitosans, and mixtures of two or more thereof.

In certain embodiments, the particle size of the droplets of the aqueous and/or non-aqueous solution or of the powders delivered to the nasal mucosa can be, for example, about 0.1 micron to about 100 microns; from about 1 micron to about 70 microns; from about 5 microns to about 50 microns; or from about 10 microns to about 20 microns. The particle sizes can be obtained using suitable containers or metering devices known in the art. Exemplary devices include mechanical pumps in which delivery is made by movement of a piston; compressed air mechanisms in which delivery is made by hand pumping air into the container; compressed gas (e.g., nitrogen) techniques in which delivery is made by the controlled release of a compressed gas in the sealed container; liquefied propellant techniques in which a low boiling liquid hydrocarbon (e.g., butane) is vaporized to exert a pressure and force the composition through the metered valve; and the like. Powders may be administered, for example, in such a manner that they are placed in a capsule that is then set in an inhalation or insufflation device. A needle is penetrated through the capsule to make pores at the top and the bottom of the capsule and air is sent to blow out the powder particles. Powder formulation can also be administered in a jet-spray of an inert gas or suspended in liquid organic fluids.

In one embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor dispersed in a nasal delivery system that improves the solubility of the proton pump inhibitor. The nasal delivery system that improves solubility can include one of the following or combinations thereof: (i) a glycol derivative (e.g., propylene glycol, polyethylene glycol, mixtures thereof); (ii) a sugar alcohol (e.g., mannitol, xylitol, mixtures thereof); (iii) glycerin; (iv) a glycol derivative (e.g., propylene glycol, polyethylene glycol or mixtures thereof) and glycerin; (v) ascorbic acid and water; (vi) sodium ascorbate and water; or (vii) sodium metabisulfite and water.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally further comprise surfactants, preservatives, antioxidants, bio-adhesives, pH

adjusting agents, isotonicity agents, solubilizing agents, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one solubilizing agent, at least one pharmaceutically acceptable thickening agent and at least one humectant. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, surfactants, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, and at least one surfactant. The nasal delivery system can optionally further comprise pH adjusting agents, isotonicity agents, solubilizing agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In yet another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

In yet another embodiment, the invention provides a nasally administrable pharmaceutical composition comprising at least one proton pump inhibitor and a nasal delivery system, where the nasal delivery system comprises at least one buffer to maintain the pH of the proton pump inhibitor, at least one pharmaceutically acceptable thickening agent, at least one humectant, at least one surfactant, and at least one solubilizing agent. The nasal delivery system can optionally further comprise buffers, pH adjusting agents, isotonicity agents, preservatives, antioxidants, bio-adhesives, and/or other pharmaceutically acceptable excipients. The proton pump inhibitor can optionally be dispersed in a nasal delivery system that improves its solubility.

The nasally administrable pharmaceutical compositions of the invention preferably provide a peak plasma concentration of the proton pump inhibitor in less than one hour, preferably within about 5

minutes to about 30 minutes, more preferably within about 5 minutes to about 20 minutes, after administration to the patient.

The buffer has a pH that is selected to optimize the absorption of the proton pump inhibitor across the nasal mucosa. The particular pH of the buffer can vary depending upon the particular nasal delivery formulation as well as the specific proton pump inhibitor selected. Buffers that are suitable for use in the invention include acetate (e.g., sodium acetate), citrate (e.g., sodium citrate dihydrate), phthalate, borate, prolamine, trolamine, carbonate, phosphate (e.g., monopotassium phosphate, disodium phosphate), and mixtures of two or more thereof.

The pH of the compositions should be maintained from about 3.0 to about 10.0. Compositions having a pH of less than about 3.0 or greater than about 10.0 can increase the risk of irritating the nasal mucosa of the patient. Further, it is preferable that the pH of the compositions be maintained from about 3.0 to about 9.0. With respect to the non-aqueous nasal formulations, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa.

The solubilizing agent for use in the compositions of the invention can be any known in the art, such as carboxylic acids and salts thereof. Exemplary carboxylic acid salts include acetate, gluconate, ascorbate, citrate, fumurate, lactate, tartrate, malate, maleate, succinate, or mixtures of two or more thereof.

The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. For example, the viscosity may be at least 1000 cps; from about 1000 to about 10,000 cps; from about 2000 cps to about 6500 cps; or from about 2500 cps to about 5000 cps. Thickening agents that can be used in accordance with the present invention include, for example, methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans, and mixtures of two or more thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation.

The nasally administrable compositions can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used include, for example, sorbitol, mineral oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and mixtures of two or more thereof. The concentration of the humectant will vary depending upon the agent selected. In one embodiment, the humectant can be present in the nasal delivery system in a concentration ranging from about 0.01% to about 20% by weight of the composition.

In other embodiments, the nasal delivery system can further comprise surfactants which enhance the absorption of the proton pump inhibitor. Suitable surfactants include non-ionic, anionic

and cationic surfactants. Exemplary surfactants include oleic acid, polyoxyethylene derivatives of fatty acids, partial esters of sorbitol anhydride, such as for example, Tweens (e.g., Tween 80, Tween 40, Tween 20), Spans (e.g., Span 40, Span 80, Span 20), polyoxyl 40 stearate, polyoxy ethylene 50 stearate, fusieates, bile salts, octoxynol, and mixtures of two or more thereof. Exemplary anionic surfactants include salts of long chain hydrocarbons (e.g., C_{6-30} or C_{10-20}) having one or more of the following functional groups: carboxylates; sulfonates; and sulfates. Salts of long chain hydrocarbons having sulfate functional groups are preferred, such as sodium cetostearyl sulfate, sodium dodecyl sulfate and sodium tetradecyl sulfate. One particularly preferred anionic surfactant is sodium lauryl sulfate (i.e., sodium dodecyl sulfate). The surfactants can be present in an amount from about 0.001% to about 50% by weight, or from about 0.001% to about 20% by weight.

The pharmaceutical compositions of the invention may further comprise an isotonicity agent, such as sodium chloride, dextrose, boric acid, sodium tartrate or other inorganic or organic solutes.

The nasal pharmaceutical compositions of the invention can optionally be used in combination with a pH adjusting agent. Exemplary pH adjusting agents include sulfuric acid, sodium hydroxide, hydrochloric acid, and the like.

To extend shelf life, preservatives can be added to the nasally administrable compositions. Suitable preservatives that can be used include benzyl alcohol, parabens, thimerosal, chlorobutanol, benzalkonium chloride, or mixtures of two or more thereof. Preferably benzalkonium chloride is used. Typically, the preservative will be present in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

Other ingredients which extend shelf life can be added such as for example, antioxidants. Some examples of antioxidants include sodium metabisulfite, potassium metabisulfite, ascorbyl palmitate and the like. Typically, the antioxidant will be present in the compositions in a concentration of from about 0.001% up to about 5% by weight of the total composition.

Other optional ingredients can also be incorporated into the nasal delivery system provided that they do not interfere with the action of the proton pump inhibitor or significantly decrease the absorption of the proton pump inhibitor across the nasal mucosa.

The nasal delivery systems can be made following the processes described in, for example, U.S. Patent Nos. 6,451,848, 6,436,950, and 5,874,450, and WO 00/00199, the disclosures of which are incorporated by reference herein in their entirety.

The invention provides pharmaceutical kits comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compounds and/or compositions of the invention, including, one or more proton pump inhibitors (e.g., rabeprazole, stereoisomers thereof and/or pharmaceutically acceptable salts thereof) and/or histamine antagonists, antacids, bismuth compounds,

sucralfate, cisapride, misoprostol, NSAIDs, migraine drugs, anti-viral agents and/or anti-fungal agents. The proton pump inhibitors and/or histamine antagonists, antacids, bismuth compounds, sucralfate, cisapride, misoprostol, NSAIDs, migraine drugs, anti-viral agents and/or anti-fungal agents can be separate components in the kit or can be in the form of a composition in the kit. The kits can also include, for example, other compounds and/or compositions, a device(s) for administering the compounds and/or compositions, and written instructions in a form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals.

While the proton pump inhibitors of the invention can be administered as the sole active pharmaceutical agent in the methods described herein, they can also be used in combination with one or more compounds which are known to be therapeutically effective against the specific disease that one is targeting for treatment.

Each of the patents and publications cited herein are incorporated by reference herein in their entirety.

It will be apparent to one skilled in the art that various modifications can be made to the invention without departing from the spirit or scope of the appended claims.

Claims

What is claimed is:

1. A nasally administrable pharmaceutical composition comprising a therapeutically effective amount of at least one proton pump inhibitor and a nasal delivery system.

2. The nasally administrable pharmaceutical composition of claim 1, wherein the nasal delivery system comprises (i) a glycol derivative; (ii) a sugar alcohol; (iii) glycerin; (iv) a glycol derivative and glycerin; (v) ascorbic acid and water; (vi) sodium ascorbate and water; (vii) sodium metabisulfite and water; or (viii) a mixture of two or more thereof.

3. The nasally administrable pharmaceutical composition of claim 1, further comprising at least one compound selected from the group consisting of a histamine antagonist, an antacid, a bismuth compound, an anti-viral agent, an anti-fungal agent, a nonsteroidal antiinflammatory drug, a steroid, and a migraine drug.

4. A method of treating a migraine in a patient in need thereof comprising administering the nasally administrable pharmaceutical composition of claim 1.

5. A transdermal patch comprising a therapeutically effective amount of at least one proton pump inhibitor and a transdermal patch system.

6. The transdermal patch of claim 5, wherein the transdermal patch system comprises a backing layer, a penetration enhancer, an adhesive, a rate-controlling membrane, a polymeric matrix, an emulsifying agent, a stabilizing agent, a dispersing agent, a suspending agent, a thickening agent, a coloring agent, an adhesive, or a mixture of two or more thereof.

7. The transdermal patch of claim 5, further comprising at least one compound selected from the group consisting of a histamine antagonist, an antacid, a bismuth compound, an anti-viral agent, an anti-fungal agent, a nonsteroidal antiinflammatory drug, a steroid, and a migraine drug.

8. A pharmaceutical composition comprising a therapeutically effective amount of at least one proton pump inhibibitor and at least one cyclodextrin or cyclodextrin derivative.

9. An intermittent therapeutic method for treating gastroesophageal reflux disease, symptomatic gastroesophageal reflux disease, or symptomatic duodenal ulcer disease in a patient in need thereof comprising intermittently administering a therapeutically effective amount of at least one proton pump inhibitor.

10. The method of claim 9, further comprising administering at least one compound selected from the group consisting of a histamine antagonist, an antacid, a bismuth compound, an anti-viral agent, an anti-fungal agent, a nonsteroidal antiinflammatory drug, a steroid, and a migraine drug.

11. A method of treating a gastrointestinal disorder in a patient in need thereof comprising administering a therapeutically effective amount of a first proton pump inhibitor and at least one compound selected from the group consisting of a second proton pump inhibitor that is different from

the first proton pump inhibitor, a histamine antagonist, an antacid, a bismuth compound, sucralfate, cisapride, misoprostol, an NSAID, a steroid, an anti-viral agent, an anti-fungal agent, a cyclodextrin, a cyclodextrin derivative, or a mixture of two or more thereof.

12. The method of claim 11, wherein the gastrointestinal disorder is a *H. pylori* infection, an ulcer, erosive esophagitis, gastroesophageal reflux disease, erosive gastroesophageal reflux disease, gastritis, symptomatic GERD, pregnancy-induced GERD, a hypersecretory condition, a gastrointestinal motility disorder, Barrett's esophagus, dyspepsia, dysphagia, irritable bowel syndrome, inflammatory bowel disease, infectious enteritis, diarrhea, gastroparesis, collagenous colitis, lymphocytic colitis, short bowel syndrome, bleeding associated with short bowel syndrome, gastrointestinal bleeding, hiatal hernia, emesis, or abdominal pain.

13. The method of claim 12, wherein the ulcer is a peptic ulcer, a bleeding peptic ulcer, a stress ulcer, a stomal ulcer, a refractory ulcer, an esophageal ulcer, a post-operative ulcer, a fungal-induced ulcer or a viral-induced ulcer.

14. A method for treating Whipple's disease, a sleep disorder secondary to gastroesophageal reflux disease, sleep apnea, iron deficiency anemia, asthma, cystic fibrosis, pancreatitis, chemotherapy-induced emesis, a radiation injury to the gastrointestinal tract, a seizure disorder, a middle ear infection, obesity, a hiatal hernia, an eating disorder, post-operative aspiration, a post-operative ulcer, erosive gastroesophageal reflux disease, or a migraine in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

15. The method of claim 14, further comprising administering at least one compound selected from the group consisting of a histamine antagonist, an antacid, a bismuth compound, an anti-viral agent, an anti-fungal agent, a nonsteroidal antiinflammatory drug, a steroid, and a migraine drug.

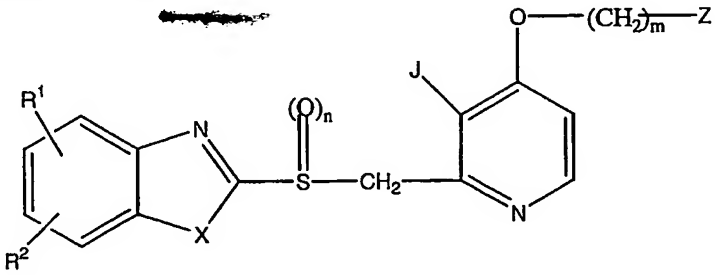
16. A method for decreasing nasal airway resistance or increasing nasal air flow in a patient in need thereof comprising administering a therapeutically effective amount of at least one proton pump inhibitor.

17. The method of claim 16, further comprising administering at least one compound selected from the group consisting of a histamine antagonist, an antacid, a bismuth compound, an anti-viral agent, an anti-fungal agent, a nonsteroidal antiinflammatory drug, a steroid, and a migraine drug.

18. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is rabeprazole, omeprazole, lansoprazole, esomeprazole, pantoprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, RO 18-5362, IY 81149, or 3-butyl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)-quinoline.

18. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16,

wherein the proton pump inhibitor is a compound of formula (I), a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof:



(I)

wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group;

X is -O-, -S- or =N-R^3, wherein R^3 is a hydrogen atom or a lower alkyl, phenyl, benzyl or lower alkoxycarbonyl group; and

Z is:

1. $-O(CH_2)_p-O-R^4$

   wherein p is an integer of 1 to 3 and R^4 is hydrogen atom or a lower alkyl, aryl or aralkyl group,

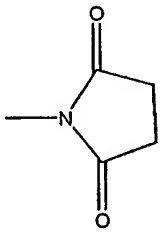
2. $-O-(CH_2)_q-R^5$

   wherein q is an integer of 1 to 3 and R^5 is a halogen atom or an alkoxycarbonyl, aryl or heteroaryl group,

3. $-O-(CH_2)_r-O-(CH_2)_s-O-R^6$

   wherein r and s are each independently an integer of 1 to 5 and R^6 is a hydrogen atom or a lower alkyl group,

4.



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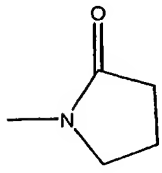

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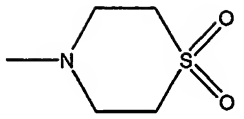
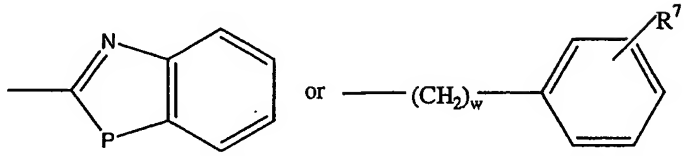


7. $-S(O)_t-A$

wherein t is an integer of 0 to 2, and A is a lower alkyl, alkoxycarbonylmethyl, pyridyl, furyl,



wherein B is -NH-, -O- or -S-, and w is an integer of 0 or 1;

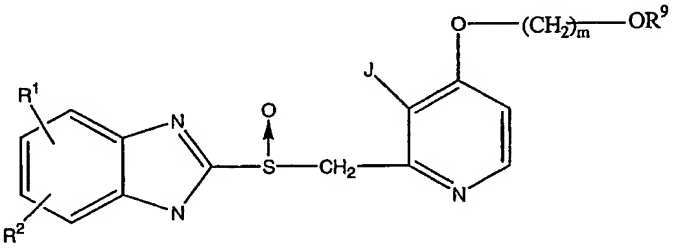
8. $-N(R^8)-CH_2-C_6H_5$

wherein R^8 is an acetoxy or lower alkyl group;

9. $-OR^9$

wherein R^9 is a hydrogen atom, a lower alkyl or aryl group; n is an integer of 0 to 2; m is an integer of 2 to 10, and J and K are each independently a hydrogen atom or a lower alkyl group, with the proviso that when Z is a group falling under the above category (9), then R^9 is a lower alkyl group and m stands for an integer of 3 to 10, and pharmaceutically acceptable salts thereof.

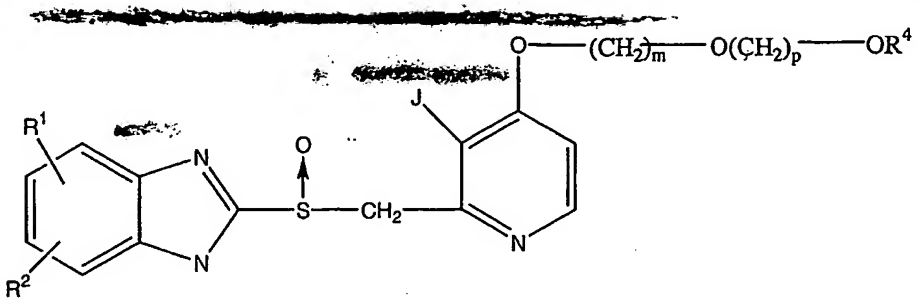
19. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is a compound of formula (A), a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof:



(A)

wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group; R^9 is a hydrogen atom, a lower alkyl or aryl group; m is an integer of 2 to 10, and J is a hydrogen atom or a lower alkyl group.

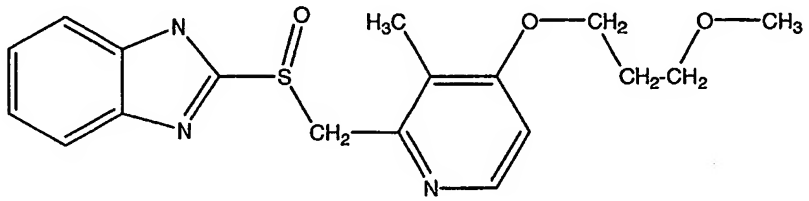
20. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is a compound of formula (B), a pharmaceutically acceptable salt thereof, and/or a stereoisomer thereof:



(B)

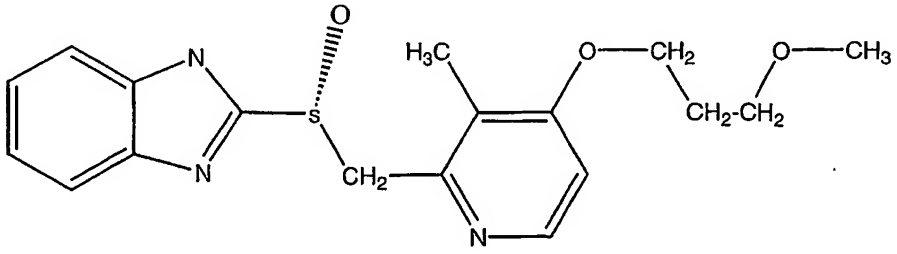
wherein R^1 and R^2 are each independently a hydrogen atom, a halogen atom, a lower alkyl, lower alkoxy, halogenated lower alkyl, lower alkoxycarbonyl or carboxyl group; R^4 is hydrogen atom or a lower alkyl, aryl or aralkyl group; R^9 is a hydrogen atom, a lower alkyl or aryl group; m is an integer of 2 to 10, and J is a hydrogen atom or a lower alkyl group.

21. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is a compound of formula (C) or a pharmaceutically acceptable salt thereof:



(C).

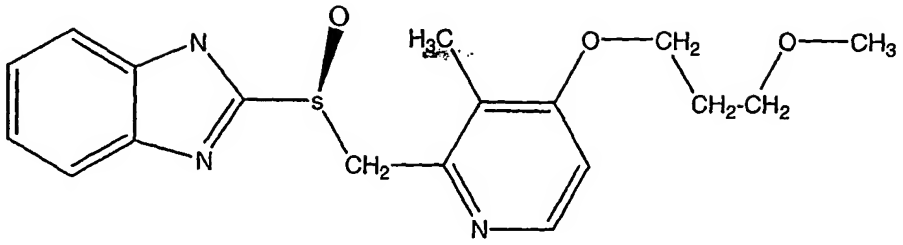
22. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is a compound of formula (D) or a pharmaceutically acceptable salt thereof:



(D).

23. The nasally administrable pharmaceutical composition of claim 1, the transdermal patch of claim 5, the pharmaceutical composition of claim 8, or the method of claim 9, 11, 14 or 16, wherein the proton pump inhibitor is a compound of formula (E) or a pharmaceutically acceptable salt

thereof:



(E).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/15308

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: 18 (both occurrences)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 18 is duplicated and in both occurrences, the dependency differs.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/15308

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A61K 9/12, 9/14, 9/72, 9/70,
US CL : 424/45, 46, 489, 443, 448
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/45, 46, 489, 443, 448, 550; 514/177, 784, 338

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN (CAPLUS, MEDLINE, BIOSIS), NPL (SCIRUS, PUB-MED, PDR), PALM

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,255,502 B1 (PENKLER et al) 03 July 2001 (03.07.2001), columns 1, 3, 4 and 9.	1-17, 19-23
Y	US 6,369,087 B1 (WHITTLE et al) 09 April 2002 (09.04.2002), entire document especially column 19.	1-17, 19-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2003 (20.08.2003)	12 SEP 2003
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer M. Haghighatian Telephone No. 703-308-0196

Form PCT/ISA/210 (second sheet) (July 1998)